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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 05/22/2002 11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/864,866	LLOYD ET AL.
	Examiner	Art Unit
	Malgorzata A. Walicka	1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *13-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

Response to restriction requirement, paper No. 9, filed on Feb. 25, 2002, is acknowledged. Applicants elected Group I, claims 1-12 with traverse.

Claims 1-40 are pending in the application. Elected claims 1-12 are the subject of this Office Action. Claims 13-40, drawn to the non-elected invention are withdrawn from consideration.

Detailed Office Action

1. Restriction /Election

Applicant's election with traverse of Group I, claims 1-12, in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the inventions, as claimed, can be readily evaluated in one search without placing undue burden on examiner. In addition, Applicants argue that a separate examination of the claims in these seven groups would require substantial duplication of work on the part of the Office. Furthermore, requiring of restriction places an undue payment of six separate filing fees for examination of the nonelected claims. This is not found persuasive because restriction involves four factors: distinctness, independence, classification and burden to the examiner.

Groups I and II, protein and DNA encoding said protein, are distinct chemical entities and require different searching of patent and non-patent literature as revealed by their different classification. Though the searches are overlapping they are not coextensive. Search of Group II would require search of class 536, subclass 23.2. which is not required for the search of Group I, which is classified in class 435 subclass 200. Thus, because of different classification, independence and different literature

search restriction between Group I and Group II is proper. Groups III, IV, V, VI and VII are distinct or independent for reasons enumerated in the previous Office action, paper No. 8. The requirement is still deemed proper and is therefore made FINAL.

Claims 13-40 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

2. Objections

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see page 12, line 5. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicants' cooperation is requested in correcting any errors of which applicant may become aware.

3. Rejections

3.1. 35 USC section 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

Claims 1-12 are rejected under 35 U.S.C. section 101, because the claimed invention is directed to non-statutory subject matter. In the absence of the hand of man,

naturally occuring proteins and/or nucleic acids are considered non-statutory subject matter. Diamond v. Chakrabarty, 206 USPQ 193(1980). This rejection may be overcome by amending the claims to contain wording such as: "An isolated and purified protein". It should be noted that a recombinat enzymes/proteins are assumed to be identical to those produced naturally unless otherwise indicated.

3.2. *35 USC, section 112, first paragraph*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Lack of written description

Claims 1-9 and 11-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are directed to any polypeptide having pyrimidine glycosylase activity or to polypeptide having pyrimidine glycosylase and at least 15% identity to SEQ ID NO: 42, 42 or 43.

The scope of the claims encompass a large genus of the pyrimidine glycosylase enzymes from any organism and man made sources. However, the specification fails to teach a structure function relationship for the claimed enzymes. The specification discloses only three species of the claimed genus, SEQ ID NO: 41, 42 and 43. This is

insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

2.2.3. Scope of eneblement

Claim 1-8 and 11-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being for enabling polypeptides having glycosylase activity and sequence selected from the group consisting of SEQ ID NO: 41, 42 and 43 does not reasonably provide enablement for any pyrimidine glycosylase or a pyrimidine glycosylase that is at least 15% identical to SEQ ID NO: 41, 42 or 43. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Neither the claims nor the specification disclose all pyrimidine glycosylases, i.e. glycosylses that are obained from any organism or man-made sources. Therefore, to make the claimed invention one skilled in the art would have to perform undue experimentation. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of invention,

(e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and the breadth of the claim.

The nature and breath of the claimed invention encompass large number of pyrimidine glycosylase obtained from any organism or a man-made sources. Although gene cloning, sequencing, manipulations, expressing in host cells, isolating of protein from host cell, measuring enzymatic activity, and protein sequencing are well known, and the skills of those in the relevant art are high, routine experimentation in the art does not include cloning, sequencing, expressing, isolation, and measuring enzymatic activity of a large number of polypeptides, from any biologic or man-made sources, and selecting those that have pyrimidine glycosylase activity and/or are in 15% identical to SEQ ID NO: 41, 42 or 43. Without the further guidance on the part of Applicants as to the source of the DNA molecules, the experimentation left to those skilled in the relevant art is undue.

3.3. 35 U.S.C. section 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1-2 are rejected under 35 U.S.C. 102(b) as being anticipated by Nilsen et al. (Nuclear and mitochondrial uracil-DNA glycosylases are generated by alternative

splicing and transcription from different positions in the UNG gene, *Nucleic Acid Research*, 1997, 25, 750-755).

Claim 1 and 2 of the instant application are directed to a peptide having pyrimidine glycosylase activity comprising a targeting sequence, wherein the targeting sequence is a nuclear or mitochondrial localization signal.

Nilsen et al. teach that human uracil-DNA glycosylase, which is a pyrimidine glycosylase, has two forms, a nuclear and mitochondral. Both forms differ from each other by the presence of different targeting sequences, nuclear and mitochondrial, at their N-termini. Nielsen and all have also shown that mitochondrial and nuclear glycosylase form are present in other mammalian cells. See the abstract of the article and sequences in Fig. 3, page 754.

Claim 3-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Otterlai et al. (Nuclear and mitochondrial splice forms of human uracil-DNA glycosylase contain a complex nuclear localisation signal and a strong classical mitochondrial localization signal, respectively, *Nucleic Acid Research*, 1998, 26, 4611-7617, enclosed in Information Disclosure Statement).

Claim 3-4 of the instant application are directed to a peptide having pyrimidine glycosylase activity comprising an exogenous targeting sequence, wherein the exogenous targeting sequence is a nuclear or mitochondrial localization signal. According to the definition on page 13, line 18, "'exogenous targeting sequence' refers to a foreign targeting sequence, i.e., a targeting sequence that is not normally fused to the polypeptide having glycosylase activity."

Otterlei et al. teach human uracil-DNA glycosylase that is engineered to contain. exogenous, (artificially mutated; substituted, deleted) targeting sequences directing the enzyme to nucleus or mitochondrium. See the abstract of the article and sequences in Fig. 2, page 4613.

3.4. *35 U.S.C. section 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 9 and 10 are rejected under 35 U.S.C. 103(a) as being unpatentable over:

(1) Lu Z. et al. (Analysis of 45 kb of DNA located at the end of the chlorella virus PBCV-1 genome, Virology (1995), 206, 339-352);

(2) Valerie K. et al. (Identification, physical map location and sequence of the denV gene from bacteriophage T4, Nucleic Acids Res. 1984, 12, 8085-8096, in Information Disclosure Statement);

(3) Piersen C. E. et al. (Purification and cloning of Micrococcus luteus ultraviolet endonuclease, an N-glycosylase/abasic lyase that proceeds via an imino enzyme–DNA intermediate, J. Biol. Chem. (1995), 270, 23475-23484, in Information Disclosure Statement);

each in view of Nielsen et al (Nuclear and mitochondrial uracil-DNA glycosylases are generated by alternative splicing and transcription from different positions in the UNG gene, *Nucleic Acid Research*, 1997, 25, 750-755) and Otterlai et al. (Nuclear and mitochondrial splice forms of human uracil-DNA glycosylase contain a complex nuclear localisation signal and a strong classical mitochondrial localization signal, respectively, Nucleic Acid Research, 1998, 26, 4611-4617, enclosed in Information Disclosure Statement).

The authors of publications (1), (2) and (3) teach the gycosylase or glycosylase/AP lyase enzymes having amino acid sequences identical to SEQ ID NO: 41, 42 and 43 of the present invention, respectively. See the enclosed results of sequence search and copies of the articles.

Publications (1) (2) and (3) do not teach the fusion of the gycosylase or glycosylase/AP lyase with sequences targeting said enzymes to nucleus or mitochondria, wherein said targeting sequences are natural or exogenous to said enzymes.

Nilsen et al teach the human gycosylases containing natural targeting sequences that targeted the enzyme to the cell nucleus or mitochondria. Otterlai et al teach the human gycosylases containing exogenous targeting sequences that target the enzyme to the cell nucleus or mitochondria.

It would have been obvious to one having ordinary skill in the art, at the time of the invention, to have the pyrimidine glycosylase or pyrimidine glycosylase/AP lyase of SEQ ID NO: 41, 42, and 43 as taught by Lu et al., Valerie et al. and Piersen et al., and

further modify these sequences by fusing targeting sequences to the enzyme as taught by Nilsen et al. or Otterlei et al., because the latter references teach that attaching targeting sequences to the instant enzymes would aid in targeting the proteins to selected cellular organs. The motivation would be to obtain a medicinal product that repairs DNA damage caused by UV light, and to make this product the most efficient by targeting to the cellular organelles when DNA is localized, i.e., to cell nucleus and mitochondria. The expectation of success in targeting the enzyme to cell nucleus or mitochondria is 100% because this process is natural in mammalian cells. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, clearly *prima facie* obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner